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26646 7590 02/13/2007 KENYON & KENYON LLP ONE BROADWAY NEW YORK, NY 10004			EXAMINER SINGH, ANOOP KUMAR	
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Please find below and/or attached an Office communication concerning this application or proceeding.

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Office Action Summary	Application No. 10/757,827	Applicant(s) ROSEN ET AL.	
	Examiner Anoop Singh	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11/20/2006.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 20, 49-51, 56, 57, 59 and 65-67 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 20, 49-51, 56-57, 59 and 65-67 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|--|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input checked="" type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>5/10/2006</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicants' amendment to the claims and specification filed September 28, 2006 has been received and entered. Applicants have amended claims 20, 49, 51, 56-57 and 59, while claims 1-19, 21-48, 52-55, 58 and 60-64 have been canceled. Applicants have also added claims 65-67 that are generally directed to elected invention.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/20/2006 has been entered.

Election/Restrictions

Applicant's election with traverse of the invention of group IV (claims 20, 23-38, 49-50 and 64) filed on October 24, 2005 was acknowledged. Applicant's argument of examining method for treating cardiac condition using composition of for ion channel transfer comprising stem cell modified with a compound (group VI, claim 51-62) with elected group were found persuasive, therefore invention of group IV and VI directed to composition and method of treating cardiac condition were rejoined for the examination purposes.

Claims 20, 49-51, 56-57, 59 and 65-67 are under consideration in the instant application.

Withdrawn- Claim Rejections - 35 USC § 112

Claims 20, 49-51, 54-57 and 59 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of amendments to the claims.

Claims 20, 49-51, 54-57 and 59 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is withdrawn in view of amendments to the claims. However, upon further consideration a new ground(s) of rejection is made under 35 U.S.C. 112, first paragraph as failing to comply with the enablement requirement commensurate with full scope of the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 49-51, 56-57, 59 and 65-67 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

(i) a method of inducing a pacemaker current in a mammal's heart, said method comprising, site specifically introducing the composition comprising a mesenchymal stem cell incorporated with a nucleic acid which encodes HCN2 ion channel in an amount sufficient to create an ion channel in the cell; wherein said composition is introduced by injection into the heart or cardiac catheterization; such that said composition forms a gap junction with the cells of the heart; thereby inducing a pacemaker current in the cells of the heart,

(ii) a method of expressing a functional HCN2 ion channel in the mammalian heart, said method comprising, site specifically introducing the composition comprising a mesenchymal stem cell incorporated with a nucleic acid which encodes HCN2 ion channel in an amount sufficient to create an ion channel in the cell; wherein said

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composition is introduced by injection into the heart or cardiac catheterization; such that said composition forms gap junction with the cells of the heart; thereby expressing the functional ion channel in the mammalian heart,

does not reasonably provide enablement for a method for treating any cardiac rhythm disorder or any method of increasing any pacemaker current in the heart or a method of expressing any other ion channel in any other syncytial structure. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The amended claims recite a method of expressing a functional ion channel in any syncytial structure comprising a MSC incorporated with a nucleic acid in amount sufficient to express HCN2 ion channel in heart. Claim 50 limits the syncytial structure to include heart. Subsequent claims recite a method of treating a cardiac condition in any subject, which comprises contacting a cell of heart with the mesenchymal stem cell incorporated with a HCN2 in an amount sufficient to increase the pacemaker current for the treatment of cardiac rhythm disorder. The claims are also drawn to a method of inducing pacemaker current in the heart of any subject by delivering the mesenchymal stem cell incorporated with HCN2 that express ion channel. The invention also encompasses a method of inducing pacemaker current in a cell which comprises contacting a cell with the composition comprising a mesenchymal stem cell incorporated with a nucleic acid which encodes HCN2 in an amount effective to induce a pacemaker current in the cell, thereby inducing a pacemaker current in the cell.

It is emphasized that although newly added claim 65 is drawn to a composition for ion channel comprising a mesenchymal stem cell incorporated with nucleic acid encoding HCN2 in an amount effective to create ion channel in the cell and deliver a pacemaker current when site specifically introduced into the syncytial structure. Since this composition is intended to be only for inducing pacemaker current in the syncytial structure, therefore it has been analyzed for its intended use in cardiac disorders.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by applicant would not have had to perform

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"undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ 1400, 2d at 1404. Such factors are: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the art; (4) The level of one of ordinary skill in the art; (5) The level of predictability in the art; (6) The amount of direction and guidance provided by Applicant; (7) The existence of working examples; and (8) The quantity of experimentation needed to make and/or use the invention.

The office has analyzed the specification in direct accordance to the factors outlines in *In re Wands*. MPEP 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on factors discussed in MPEP 2164.01(a) and the evidence as whole, it is not necessary to discuss each factor in written enablement rejection." These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

The aspects considered broad are: breadth of subject population, method of treating any cardiac rhythm disorder in any subject, expression a functional ion channel in any syncytial structure, any route and method of administering the composition subsequently limiting to injection and catheter and inducing pacemaker current in any cell.

The specification as filed provides a general description of pacemakers and cardio-active drugs and the summary of the inventions (pp 1-6). Pages 7-9 describe brief description of figures showing transfer of Lucifer yellow dye from stem cell to HeLa cell and coupling and ionic dye transfer between stem cell and a canine cardiomyocyte. Page 10-18 provides a detailed description of the invention, preferred embodiments and definitions of terms. Page 19-34 discloses a proposal in five different phases that includes for expression, regulation of pacemaker gene *in vitro*, *in vivo*, and in isolated tissue. Applicant's examples on pages 7-9 disclose the transfer of Lucifer yellow dye from stem cell to HeLa cells transfected with Cx43 showing transfer of dye by diffusion through gap junction. Figures 3(A-C) show coupling and ionic and dye transfer between

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stem cells and a canine cardiomyocyte while Figure 4(A-B) demonstrate stem cell coupling with HeLa cells. Figure 5, 6 and 8 show human mesenchymal stem cell and inward rectification, needle survival and transient transfection of MSC. Figure 8 and 9 disclose HCN2 incorporate stem cell could generate pacemaker current while Figure 10(A-E) demonstrate expression of pacemaker current in canine ventricle *in situ* as a result of implanting mesenchymal stem cell having the HCN2 pacemaker gene. In summary, the specification does not provide any specific guidance to practice claimed invention in humans because the specification as filed does not teach how to obtain MSC showing stable expression of HCN2 at therapeutic effective level for sustained period.

As a first issue, the scope of invention embrace a method for inducing expressing any functional ion channel in any syncytial structure in a mammal by administering the composition comprising MSC incorporated with a nucleic acid encoding a HCN2 ion channel gene. The breadth of instant claims embrace expressing a functional ion channel in any syncytial structure. The specification provides guidance of using hMSC as delivery vehicle only in heart for the expression of HCN2 in which hMSC expressing HCN2 is engrafted with recipient cardiomyocytes via formation of gap junction. However, in a post filing art, Popp et al (Stem Cells Express, published online November 16, 2006, 1-25) show that MSC injection directly into the portal vein of a recipient rat resulted in no engraftment of MSC in different liver injury model. This clearly provide evidence that a general method of site specific administration of MSC as delivery vehicle in any syncytial structure would not result in engraftment or formation of gap junction as contemplated by the breadth of the claim. Therefore, in absence of any specific guidance regarding expression of functional ion channel in any syncytial structure other than heart would constitute an enormous amount of experimentation to empirically test all known syncytial structure and determine if administration of composition of the instant invention would engraft with the recipient structure and express functional ion channel. As described before, the specification does not provide adequate guidance to the breadth of the claims as amended and therefore an artisan of skill would require undue experimentation to practice or make and/or use the invention.

As a second issue, the scope of invention embraces a method for inducing pacemaker current and treating a cardiac rhythm disorder in a subject by administering the disclosed genetically modified MSC composition. It has been difficult to predict the efficacy and outcome of a transplanted hMSC because several factors that governs the therapeutic potential of these cells *in vivo*. The specification exemplified a method demonstrating injection of adenoviral constructs carrying HCN2 into canine ventricular myocardium *in vivo* can elicit pacemaker current (see para 164 and 165 of the specification). The specification further contemplates to test the function of specific HCN subunit constructs inserted into human mesenchymal cell lines to provide functional pacemakers to the heart *in situ*. The breadth of instant claims 51-52 requires expression of HCN2 to at therapeutic effective level sufficient to create ion channel for a sustained period in order to treat any cardiac rhythm disorder. However, prior to instant invention, the state of the prior art effectively summarized by the references of Verma and Somia (1997) Nature 389:239-242 and Pfeifer and Verma (2001) Annual Review of Genomics and Human Genetics.2: 177-211 describes progress made in developing new vectors and also suggest vector targeting continues to be unpredictable and inefficient. Verma et al., reviews various vectors known in the art for use in gene therapy and problems associated with each implying that at the time of claimed invention resolution to vector efficiency for long term sustained expression of transgene had not been achieved in the art (Verma et al., 1997; Pfeifer et al., 2001; entire article). The specification does not provide any specific guidance as to how expression of HCN2 would be achieved at therapeutic effective level for sustained period of time using any construct. The guidance provided in specification correlates to a transient expression of HCN2 in inducing pacemaker current in heart. In addition, Potapova acknowledges, "it remains to be seen if the differentiation state of MSC is altered *in situ* or whether such differentiation would affect HCN2 expression or biophysical property (See page 959, col. 1, lines 1-3). Barry et al (The International Journal of Biochemistry of Cell Biology, 36, 568-584, 2004), while reviewing the state of MSCs in transplantation cell therapy concluded that there are several aspect to the implanted cell host cell interaction that need to be addressed before we can fully understand the host immune response to

implanted cells. The homing mechanism that guide delivered cells to the target site and the differentiation of implanted cells under the influence of local signals (abstract and pp 580, col. 2, conclusion). Additional important issues of MSCs cell therapies are the therapeutic efficacy of the transplanted cells and the mechanism of engraftment, homing and *in vivo* differentiation. Gepstein (Expert Opinion Biol Ther, 5(12); 1531-1537, 2005), while reviewing the state of stem cell as biological heart pacemaker and providing and expert opinion reports that one limitation relates to the possible differentiation of the MSCs within the heart into unwanted cell lineages, such as bone and cartilage (pp 1534, col. 1, last para). In addition, issues relating to the number and distribution of the surviving grafted cells within the heart, and the degree of coupling between the host and donor cells may have important consequences to the function of these cells (pp 1534, col. 1, last para). The specification fails to provide an enabling disclosure for the claimed invention commensurate with full scope because the specification fails to provide sufficient guidance as to how instant methods could be practiced in any mammal by administering composition of the invention via any route using any construct expressing HCN2 at therapeutic effective level for a sustained period. In addition, differentiation of MSC, non-specific engraftment and host immune response are other unpredictabilities associated with the treatment of any cardiac rhythm disorder. An artisan would have to carry out extensive experimentation to make use of the invention, and such experimentation would have been undue because sustained expression of transgene by MSC at the target site, non-specific engraftment and host immune response continues to be unpredictable and specification fails to provide any guidance as to how the claimed method would have been practiced commensurate with full scope of the claim.

As a final issue, the claimed invention embrace a method wherein contacting a MSC is effected by injection and microinjection or catheterization. Boheler et al (J Physiology, 554, 3, 592) while discussing the outcome of MSC therapy raise number of question concerning best way to introduce (local or systemic) cells for therapeutics and the survival and homing capacity of the cells to host tissues following transplantation. Gepstein reports for cell therapy approaches determining the optimal way for the

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delivery of the cell controlling their survival following transplantation, assuring appropriate integration of the cells with the host tissue and developing means to control the required effect all important obstacle for the future use of these strategies. In addition, issue related transplanted cells as well as their potential to differentiate into undesired cell lineages should be addressed (page 1536). In fact, in a post filing art, Potapova et al describe the limitation of delivery of modified hMSC to free wall myocardium that is not an optimal site of contraction. It is noted that applicants describes more ordered and normal activation and contraction using catheter approach to insert pace maker gene. In addition, Potapova et al also emphasize the importance to modifying catheter to optimize injection of MSC without cell injury and destruction (see page 958, col. 2, para. 3, Potapova et al Circulation Research, 2004, 94, 952-959). The cited art clearly suggests that administering MSC by any route and method was mere a hypothesis and an artisan would have to deliver cells via different route to determine the extent of cell injury and destruction. In view of foregoing discussion, it is evident that unpredictability related to undesired cell lineages differentiation and unordered activation and contraction would be expected if MSC are delivered via any route and method as broadly embraced by claims 49-51, 57, 59 and 65-67. An artisan would have to carry out extensive experimentation to make and use the invention, and such experimentation would have been undue because of plurality of variables associated with mesenchymal stem cell transplant therapy for a cardiac rhythm disorder and specification fails to provide any guidance as to how the claimed method would have been practiced in any mammal commensurate with full scope.

In conclusion, in view of breadth of the claims and absence of a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled for the claimed inventions commensurate with the full scope of the claims. An artisan of skill would have required undue experimentation to practice the invention because the art of cell therapy in general for the treatment of cardiac condition was unpredictable at the time of filing of this application as supported by the observations in the art record.

Response to Arguments

Applicant arguments filed on 09/28/2006 have been fully considered but they are not fully persuasive. Specifically, Applicant's amendments to claims 49, 51, 56, and 57 sufficiently addresses the ground of rejection to the extent it is limited only to a site specifically introducing the composition of the invention to mammal's heart. Therefore, instant amendments will overcome these grounds of rejection. In addition, applicants argument with respect to homogenous population of MSC (page 6, Exhibit 1), SA node cell and delivery of MSC via catheterization is found persuasive and therefore rejection pertaining to these issues are withdrawn.

However, Applicants argument regarding immune response to implanted MSC and homing mechanism is not persuasive to the extent claims are broad and embrace administering the composition site specifically into the heart. Claim 49, 51, 57, 59, 66-67 are broad and only require administering composition that could be achieved by simply by injecting into any blood vessel. However, cited references teach mechanism of engraftment, homing and *in vivo* differentiation are critical determinant for using MSC in any therapy (see office action mailed supra). Furthermore, Gepstein (Expert Opinion Biol Ther, 5(12); 1531-1537, 2005, art of record) reports importance of determining the optimal way for the delivery of the cell and controlling their survival following transplantation, assuring appropriate integration of the cells with the host tissue and developing means to required effect are other issue related with transplanting MSC. Applicants provide specific guidance to a very specific method to induce current in the heart of a mammal using MSC that is administered via a specific route and mode. In the instant case, Applicants provide no evidence to support that cited exhibits or examples would necessarily enable a method of inducing current or express ion channel using a composition that is delivered via any route into the heart and is not required to form any gap junction of expression of HCN2 at the site of engraftment. The specification only provides guidance for administering composition using a specific construct for a specific period by administering the composition via injection/catheterization (supra). The art teaches unpredictability of using viral vectors for achieving sustained expression,

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differentiation of MSC after prolonged engraftment in heart, homing mechanism and other unpredictabilities associated with resulting effect after administration of composition via any route and method that would require further experimentation in the treatment of any cardiac rhythm disorder. Absent of evidence to the contrary, it is not clear that these elements would be functional in achieving contemplated biological effects in the same manner as they have been demonstrated in the instant method. It is noted that the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991). It is also well established in case law that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. *In re Goodman*, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing *In re Vaeck*, 20 USPQ2d at 1445 (Fed. Cir. 1991). An artisan would have to perform undue experimentation to determine whether delivery of composition to any syncytial structure delivered via any route or mode would result in expression of ion channel or increase a pacemaker current in the heart as broadly recited in this application.

On page 17, in the second paragraph, applicants argue that instant ground of rejection appears to be based on the absence of an optimized protocol in the specification for performing claimed methods. In response, it is emphasized that instant rejections are because of lack of disclosure of specifics commensurate with full scope of the claimed invention. Further, the specification also provided no correlation between number of stem cell delivered that are engrafted at the site of action to number of cells that are relocated to other places (previous office action, page 7, para. 3). It is noted that the amendment in instant claims now recite composition comprising modified MSC. The issue of effective number of cell engraftment in heart is critical to overall biological effect contemplated in the specification. The specification does not address the art-recognized limitations of expressing a transgene, delivered via MSC resulting in sustained expression of HCN2 at therapeutic level. It is emphasized that prior art teaches homing, degree of engraftment and differentiation of MSC to other lineage after prolonged engraftment are other important factor that remains unpredictable in the

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treatment of cardiac rhythm disorder (supra). These factors are not optimization factors rather are directly relevant to the therapeutics of the claimed invention. It is emphasized that specification and examples at best provide adequate guidance to a method of inducing pacemaker current in a mammal heart, however specification provides no conclusive evidence that such a method would result in the treatment of plurality of disorder as broadly recited in claim 51.

Withdrawn-Claim Rejection - 35 USC § 103

Applicant's arguments, see pages 19-22, filed September 28, 2006, with respect to the rejection(s) of claim 20 under 35 U.S.C. 103(a) have been fully considered and are persuasive. Therefore, claim 20 rejected under 35 U.S.C. 103(a) as being unpatentable over Marban et al (US Patent application Publication no US2004/0254134, publication date 2/16/2004; effective filing date 2/29/2002) and Heubach et al (Circulation, 106 (19) 2002, suppl. pp II-68), Jansen et al (US Patent no 6979532, dated 12/27/2005, effective filing date 2/12/2000) is withdrawn. However, upon further consideration, a new ground(s) of rejection is made.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 20, 49-50, 57, 58 and 65-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Levy et al (US patent application 20040087528, dated 5/6/2004, effective filing 4/24/2002); Marban et al (US Patent application Publication no US2004/0254134, publication date 2/16/2004; effective filing date 2/29/2002, art of

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record); Jansen et al (US Patent no 6979532, dated 12/27/2005, effective filing date 2/12/2000, art of record); Wang et al (J Thorac Cardiovasc Surg. 2000; 120(5): 999-1005).

Levy et al describe reverse gene therapy wherein a gene therapy vector encoding a gene product is expressed in cells of an abnormal tissue of an animal to alleviate the disease (see abstract). It is noted that Levy et al also teach compositions and a method for providing progenitor cells including MSC, comprising a disease-related polynucleotide, such that cells express the polynucleotide upon administering an effective amount of cells comprising polynucleotide at the diseased site (See para 27, 31 and 109 and of the published application). Levy et al also teach delivery of transformed cells to the diseased site by localized infusion or by direct injection of a suspension of transformed cells (see para. 72 of the published application). Although, Levy et al do not teach administering a composition of MSC comprising HCN2 but he generally embraced the idea of delivering genetically modified MSC comprising therapeutic (e.g. ion channel mutation) for the treatment of cardiac disorders.

Marban et al discloses a composition of modified cells and a method comprising administration of genetically modified composition to induce or modulate pacemaker activity in a subject. It is noted that source of modified cells are cardiac myocardial cells generated from differentiated stem cells, such as embryonic bone marrow cells. The stem-cell-derived cardiomyocytes exhibiting pacemaker function then may be implanted such as by catheter or injection to targeted cardiac tissue (page10, paragraph 121 and paragraph 26). Marban also teach genes that could be used to affect cardiac firing rate includes ion channels including HCN channels (page 6, paragraph 64). The teaching of Marban et al encompasses HCN2 channel as different isoform of HCN channel were known in the art and Marban et al intend to use different HCN channels to affect firing rate of heart. However, Marban et al do not teach using a composition comprising MSC comprising HCN2.

Jansen et al teach a process comprising providing mammalian cells that express a hyperpolarization-activated cation channel including HCN2 and determining the membrane potential of the cells (col. 5, lines 5-25, col. 5, lines 60-63 and claims 1, 21

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and 31. However, Jansen et al do not explicitly teach a composition of MSC comprising HCN2.

Wang et al teach administration of MSC in the heart shows growth potential in a myocardial environment and indicates the formation of gap junctions suggesting that cells derived from marrow stromal cells, as well as native cardiomyocytes, are connected by intercalated disks (see abstract and Figure 6). However, Wang et al do not teach composition-comprising MSC comprising HCN2.

It would have been obvious for one of ordinary skill in the art at the time of invention to modify the MSC cells taught by Levy et al to include other ion channels such as HCN2 taught by Marban et al, for using MSC as delivery vehicle to express HCN2 in mammalian heart for pacemaker activity. Marban and Jansen provided motivation to transfect cells with HCN channels gene as, it was generally known to one skilled in the art that HCN2 could be used to affect cardiac firing rate. The skilled artisan would be motivated to use different isoforms of HCN including HCN2 as Jansen had already shown that HCN2 could be expressed in mammalian cells to determine membrane potential and Marban had disclosed the usefulness of HCN channel gene in pacemaker activity. In addition, the skilled artisan would be motivated to make such a modification particularly since Wang taught hMSCs engrafts in the myocardium and forms gap junction with recipient cells (supra).

One who would practice the invention would have reasonable expectation of successfully practicing the method and composition comprising mesenchymal stem cell incorporated with HCN2 or other ion channel gene because the art had already shown that HCN2 and other ion channel isoform could be expressed in different cardiac or stem cell for pacemaker activity. Furthermore, Levy generally embraced the idea of using directly injecting MSC for delivering polynucleotide for the treatment of cardiac disorder, while Wang disclosed that implanted MSC form gap junction in myocardium environment. In addition, Marban taught that cardiac pacing, and subsequent heart rate, could be effectively induced by over expression of nucleotide gated (HCN) gene expression (see Marban et al, para. 20 of the published application). One of ordinary skill in art would have been motivated to combine the teaching of Levy, Marban, Jansen

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and Wang, because a direct administration of the composition comprising mesenchymal stem cell comprising nucleic acid encoding HCN2 into the heart by injection would have led to the engraftment of MSC with recipient heart cells resulting in expression of HCN2 and thereby induction in pacemaker current at the delivery site.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Claims 20 and 65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marban et al (US Patent application Publication no US2004/0254134, publication date 2/16/2004; effective filing date 2/29/2002, art of record); Jansen et al (US Patent no 6979532, dated 12/27/2005, effective filing date 2/12/2000, art of record); Wang et al (J Thorac Cardiovasc Surg. 2000; 120(5): 999-1005) and Ruhparwar et al (Eur J Cardiothorac Surg. 2002; 21(5): 853-7, IDS),

The combined teaching of Marban et al, Jansen et al and Wang et al is same as presented before and relied in same manner here.

Prior to instant invention, Ruhparwar et al teach a method comprising administering cardiomyocytes (2×10^6) directly into the free wall of the left ventricle of adult canine X-linked muscular dystrophy dogs that fail to express Dystrophin in cardiac muscle. It is noted that Ruhparwar et al teach that transplanted cells are identified by integration in the recipient heart. The expression of Connexin 43 between donor and recipient cells suggested formation of gap junctions between injected and host cardiomyocytes (see page 855, col. 1, para. 1). After catheter ablation of the AV-node, a ventricular escape rhythm emerged driving the pace of the heart and originating from the labeled transplantation site. Thus, teaching of Ruhparwar et al shows electrical and mechanical coupling between allogeneic donor cardiomyocytes and recipient myocardium in-vivo (see abstract). It is noted that Ruhparwar et al emphasizes that cardiomyocytes engraftment could initiate further research aiming at generation of autologous cardiomyocytes preferably from pluripotent embryonic or adult stem cells or

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by achieving controlled proliferation of adult cardiomyocytes (see page 857, col. 1, last paragraph). However, Ruhparwar et al do not teach a composition comprising MSC comprising HCN2 or method of using such composition.

It would have been obvious for one of ordinary skill in the art at the time of invention to modify the cells taught by Marban et al by expressing a nucleic acid encoding specific HCN isoforms for expressing ion channel genes in stem cell at sufficient level for pacemaker activity. Marban provided motivation to transfect cells with HCN channels gene as, it could be used to affect cardiac firing rate. The skilled artisan would be motivated to use different isoforms of HCN including HCN2 as Jansen had already shown that HCN2 could be expressed in mammalian cells to determine membrane potential and Marban had disclosed the usefulness of HCN channel gene in pacemaker activity. The skilled artisan would be motivated to modify the cardiomyocytes/embryonic bone marrow cell comprising HCN2 channel gene with MSC cells disclosed by Wang et al. The skilled artisan would be motivated to make such a modification particularly since Wang taught that hMSCs could engrafts in the myocardium and form gap junctions after implantation in a myocardial environment (supra). Ruhparwar et al taught electrical and mechanical coupling between allogeneic donor cardiomyocytes and recipient myocardium *in-vivo*.

One who would practice the invention would have reasonable expectation of successfully producing a composition comprising mesenchymal stem cell incorporated with HCN2 or other ion channel gene because the art had already shown that HCN2 and other ion channel isoform could be expressed in different cardiac or stem cell for pacemaker activity. Furthermore, Wang taught that MSC engrafts and for gap junction in myocardium, while Ruhparwar et al showed the formation of gap junction between the donor and recipient cells resulting in electrical and mechanical coupling. One of ordinary skill in art would have been motivated to combine the teaching of Marban, Jansen, Wang and Ruhparwar et al because administration of the composition comprising mesenchymal stem cell comprising HCN2 would have resulted in engraftment and formation of gap junction between the MSC/differentiated cardiomyocytes with recipient heart cells to for form ion channel.

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Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Maintained -Double Patenting

Claims 20, 49-51, 54-57 and 59 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 20-59 of copending Application no 10/342506 (US Patent Publication no 20040137621). Even though the conflicting claims are not the same, they are not patentably distinct from each other because both sets of claims encompass similar composition and a method of inducing current and a method of treating a cardiac condition by introducing a composition of mesenchymal stem cell comprising a nucleic acid encoding HCN2 into a subject.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. As indicated by applicants a Terminal disclaimer later would obviate this rejection.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

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Conclusion

No Claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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